AMENDMENT TO THE DRAWINGS

The attached 23 sheets of drawings **(Appendix A)** are formal versions of the informal drawings submitted at the time of filing for Figures 1-12.

REMARKS

I. Preliminary Remarks Regarding Amendments

By the foregoing, the Applicants have amended the specification to Figures 1A-1L for original Figure 1. Also submitted herewith is one set (23 sheets, Figures 1-12) of formal drawings for filing in the above-identified patent application. Kindly substitute the enclosed formal drawings for the informal drawings submitted with the originally filed application. Although the drawings were indicated to be acceptable by the Examiner in this Office Action, the Applicants are submitting revised drawings, in conformity with the prosecution in parent application, U.S. Serial No. 09/724,126, now U.S. Patent No. 6,706,505, issued March 16, 2004.

Claims 9, 12-14, 16-18, 40-45, 49, 50, and 58 are currently pending and claims 13, 14, 16-18, 40-45, 49, and 50 are under examination. Claim 13 has been allowed. Claims 9, 12, and 58 have been withdrawn from consideration for assertedly being drawn to a non-elected invention, but are currently amended to be consistent in format with claims under examination. Claims 14, 16, 17, 40, 43, and 49 are amended herein. Claims 14, 16-18, 40-45, 49, and 50 were rejected under 35 U.S.C. §102(b) and §112, first paragraph (written description and enablement).

Claims 9, 12, 14, 16, and 17 have been amended to replace the abbreviated term "huE3α" with the unabbreviated term "human E3α ubiquitin ligase." Support for this amendment is found throughout the specification, including at page 1, lines 9-10.

Claim 14 has been amended to recite an isolated polypeptide comprising the amino acid sequence that is at least 95 percent identical to the amino acid sequence of SEQ ID NO: 2, wherein the encoded polypeptide has human E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 2, thus providing structural and functional characteristics sufficient to identify members of the claimed genus. Support in the specification for a human E3 α ubiquitin ligase polypeptide that is at least 95 percent identical to the amino acid sequence of SEQ ID NO: 2 is found at least at page 11, lines 9-15. Support in the specification for human E3 α ubiquitin ligase activity is found at least at page 2, line 8 through page 4, line 14. The specification describes how E3 α ubiquitin ligase functions in the proteosomal pathway.

Claim 16 has been amended to recite an isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2 with modifications of one to 100 amino acids

consisting of amino acid substitutions, amino acid insertions, amino acid deletions, and C- and/or N- terminal truncations up to about 100 amino acids, wherein the polypeptide has human E3 α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 2, thus providing structural and functional characteristics sufficient to identify members of the claimed genus. Support in the specification for variants of human E3 α ubiquitin ligase polypeptide with modifications of from one to 100 amino acids is found at page 17, lines 14-32. Support in the specification for human E3 α ubiquitin ligase activity is found at page 2, line 8 through page 4, line 14.

Claim 17 has been amended to recite the stringent conditions necessary for hybridization, along with polypeptide activity, thus providing structural and functional characteristics sufficient to identify members of the claimed genus. Support in the specification for the recited hybridization conditions is found at page 14, line 27, through page 16, line 20. Support in the specification for human E3 α ubiquitin ligase activity is found at page 2, line 8 through page 4, line 14. Claim 17 has also been amended to recite that the nucleotide sequence of subpart (c) hybridizes under expressly recited highly stringent conditions to the complement of the coding sequence of (a) or (b). Claims 17 has been further amended to recite that the nucleotide sequence of subpart (d) is fully complementary any of (a)-(c). Support in the specification for "fully complementary" sequences is found at page 11, lines 27-31.

Claims 40, 43, 49, and 58 have been amended to depend on claims 13, 14, 16, or 17. Claim 43 has been amended to recite "a chemically modified derivative of the polypeptide of claim 13, 14, 16, or 17. Claim 44 has been amended to depend on the polypeptide derivative of claim 43. Support for these amendments is found in the original claims and in the specification at page 24, line 1, through page 25, line 23.

No new matter is introduced by the substitute figures, the references thereto added to the amended specification, or the amended claims. Support for the amendments is found throughout the specification and the original claims as filed.

The Applicants do not intend, with these or any other amendments, to abandon the subject matter of claims previously presented, and reserve the right to pursue such subject matter in duly filed continuing patent applications.

II. Patentability Remarks

A. The Rejection under 35 U.S.C. §102(b) May Properly Be Withdrawn.

The Patent Office rejected all pending claims under 35 U.S.C. § 102(b) as assertedy being anticipated by Kwon et al., *Proc. Natl. Acad. Sci. U.S.A.* 95:7898-7903, 1998 (cited in the Applicants' Information Disclosure Statement); hereinafter "Kwon." Office Action at page 10. Kwon apparently discloses the mouse ortholog of human ubiquitin ligase E3α polypeptide, which assertedly consists of 1757 amino acids and is 93.4% identical to SEQ ID NO: 2. Based on that characterization, the Examiner asserted that the DNA which encodes the protein thereof will hybridize to SEQ ID NO: 1 under highly stringent conditions. In response, the Applicants disagree.

To invalidate a claim for "anticipation" under 35 U.S.C. § 102, a single reference must identify each and every feature recited in the claim sought to be invalidated. *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991).

The Applicants submit that Kwon does not disclose each and every feature recited in the pending claims. Contrary to the Examiner's assertion that Kwon teaches the mouse ortholog of SEQ ID NO: 2 that is 93.4% identical to SEQ ID NO: 2 (*see* page 10 of the Office Action), the polypeptide sequence disclosed by Kwon appears to share at most 92% identity to the polypeptide of SEQ ID NO: 2 (see alignment set forth in **Appendix B;** as aligned using the online BLAST program provided by the National Center for Biotechnology Information at http://www.ncbi.nlm.hih.gov/blast/bl2seq). Thus, the Applicants submit that the claims, as amended, exclude the subject matter described by Kwon. For example, the murine UBR1 polypeptide of Kwon fails to anticipate a polypeptide having 95% identity to the amino acid sequence of SEQ ID NO: 2, as recited in claim 14. The murine UBR1 polypeptide of Kwon, which assertedly shares 1619/1757 (92%) amino acid identity with SEQ ID NO: 2 (*see* **Appendix B**), also fails to anticipate the subject matter of claim 16, which discloses human E3α ubiquitin ligase variants of SEQ ID NO: 2 with up to 100 amino acid modifications comprising substitutions, insertions, deletions, C-terminal truncations, and/or N-terminal truncations. Moreover, Kwon's mouse ubiquitin ligase E3α polynucleotide sequence will not hybridize to SEQ ID NO: 1 under the highly stringent conditions recited in claim 17.

Thus, Kwon fails to disclose, expressly or inherently, each limitation of any one of the rejected claims. Accordingly, Kwon fails to anticipate the subject matter of any of the rejected claims. For these reasons, the rejection of claims 14, 16-18, 40-45, 49, and 50 under 35 U.S.C. § 102(b) has been overcome and should be withdrawn.

B. The Rejections Under 35 U.S.C. 112, First Paragraph, May Properly Be Withdrawn.

1. Written Description

The Patent Office rejected claims 14, 16-18, 40, 41, 43-45, 49, and 50 under 35 U.S.C. § 112, first paragraph, for allegedly lacking adequate written description. Office Action at pages 4-6. The Examiner has asserted the following reasons for rejection: 1) claim 14 (b) recites "an ortholog of SEQ ID NO: 2 and claim 14 (c) [apparently the Examiner meant to recite 14 (e)] recites an allelic or splice variant of either the amino acid sequence as set forth in SEQ ID NO: 2, or at least one of (a)-(c), and the Applicants have described only one member of the claimed genus and has not described how the structure of SEQ ID NO: 1 relates to the structure of other allelic or splice variants; 2) claim 16 lacks limitations on the number of modifications that can be made to the polypeptides having the amino acid sequence of SEQ ID NO: 2 with at least one conservative substitution, insertion, deletion, truncation, or a combination of the above and, therefore, fails to provide a sufficient description of the claimed genus in structure and function to identify members of the genus; and 3) the specification fails to provide any structure:function correlation present in all members of the claimed genus.

The Examiner also relied on *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) whereby a claimed genus must (1) fully describe at least one species whereby one of skill, in view of the prior art, could predict the structure of other species encompassed by the claimed genus, and (2) identify the common characteristics of the claimed molecules. The Examiner provided reasons for rejecting independent claims 14 and 16, but did not provide a reason for rejecting independent claim 17 or dependent claims 18, 40, 41, 43-45, 49, and 50 for lack of written description. Office Action at page 6. The Applicants respectfully traverse this rejection

and submit that the claimed subject matter, as originally filed, is adequately described in the specification.

To satisfy the written description requirement under 35 U.S.C. §112, first paragraph, the application as filed must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ.2d 1111 (Fed. Cir. 1991); *see also* M.P.E.P. §2163 (I). Moreover, the initial burden of establishing a *prima facie* case of lack of written descriptive support is on the Office. M.P.E.P. §2163 (II). The Applicants submit that the Patent Office has not met this burden. Moreover, the basis alleged for this rejection is now moot in consideration of the amendments to the claims.

To expedite prosecution, the Applicants have 1) amended claim 14 to remove reference to orthologs and allelic or splice variants and to recite the specific polypeptide activity as being "human E3α ligase activity"; 2) amended claim 16 to include a limitation on the number of modifications that can be made to the polypeptide having the amino acid sequence of SEQ ID NO: 2 and to recite the specific polypeptide activity as being "human E3α ligase activity"; and 3) amended claim 17 to include the specific hybridization conditions necessary defining members of the claimed genus and to recite the specific polypeptide activity as being "human E3α ligase activity." These amendments provide structural and functional attributions to define members of the claimed genus, thereby overcoming the bases for rejection.

Specifically, claim 14 has been amended to recite an isolated polypeptide comprising an amino acid sequence that is at least 95 percent identical to the amino acid sequence of SEQ ID NO: 2, wherein the encoded polypeptide has human E3α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 2, thus providing structural and functional characteristics sufficient to identify members of the claimed genus. Support in the specification for human E3α ubiquitin ligase activity is found at page 2, line 8, through page 4, line 14, wherein the specification describes how E3α ubiquitin ligase functions in the proteosomal pathway. Also, contrary to the Examiner's assertion that the Applicants have only provided one allele within the scope of the claimed genus (SEQ ID NO: 2 encoded by SEQ ID NO: 1) (*see* Office Action at page 4), the Applicants note that the specification teaches an allelic variant of SEQ ID NO: 1, namely SEQ ID NO: 18, with a single nucleotide polymorphism (SNP) that

encodes a polypeptide variant of SEQ ID NO: 2 (SEQ ID NO: 19) (*see* Example 9, page 97, line 23 through page 98, line 12). Thus, the specification provides written descriptive support for two alleles of human E3α ligase within the scope of the claimed genus: two polynucleotides (SEQ ID NOS: 1 and 2) which encode two polypeptides (SEQ ID NOS: 18 and 19, respectively). The claims require that these and other allelic variants possess substantial sequence identity which defines the genus. Further, Figure 1 provides an alignment of the amino acid sequences for human and murine E3α ubiquitin ligases I and II and, thus, identifies regions of the polypeptides that are highly conserved. Further, conservative amino acid substitutions in polypeptides and the redundancy of the genetic code are well known facts in the art that are effectively described by reciting "variants". Taken together, one of skill in the art would recognize that the Applicants were in possession of the claimed genus.

Claim 16 has been amended to recite a nucleotide sequence encoding a polypeptide set forth in SEQ ID NO: 2 with modifications of one to 100 amino acids consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncation, and/or N-terminal truncation, wherein the polypeptide has human E3 α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 2, thus providing structural and functional characteristics sufficient to identify members of the claimed genus.

The rejection of claim 17, although not specifically supported by rejection for a lack of written description in the Office Action, has been amended to recite the stringent conditions necessary for hybridization and to recite the polypeptide activity (human E3α ubiquitin ligase activity), thus providing structural and functional characteristics sufficient to identify members of the claimed genus.

In summary, the Applicants submit that amended claims 14, 16, and 17 are described sufficiently by one of skill to reasonably conclude that the inventors were in possession of the claimed genera as of the relevant filing date. Consequently, the rejections under 35 U.S.C. § 112, first paragraph, for lack of written description have been overcome-in-part and are rendered moot-in-part by the amendments to the claims. Moreover, the rejection as it pertains to claims 17, 18, 40, 41, 43-45, 49, and 50 should be withdrawn for failure to establish a *prima facie* basis or any basis, for rejection under 35 U.S.C. § 112, first paragraph, for lack of written description.

2. Enablement

Claims 14, 16-18, 40-45, 49, and 50 were rejected under 35 U.S.C § 112, first paragraph, for assertedly not providing enablement for the broad scope of claims which encompass polypeptides having an amino acid sequence at least 70, 80, 85, 90, or 95% identical to the amino acid sequence of SEQ ID NO: 2 or having no known percent identity to SEQ ID NO: 2 and retaining E3 α ubiquitin ligase activity. The Examiner also rejected the claims for encompassing polypeptides having no defined activity or having E3 α ubiquitin ligase activity that is encoded by a nucleotide sequence that hybridizes under highly stringent conditions to SEQ ID NO: 1. The Examiner then recited the Wands factors (*see In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)) as factors to be considered in determining whether undue experimentation is required. Office Action at pages 6-8. The Applicants respectfully traverse this rejection and submit that the claims, as originally filed, are fully enabled by the specification.

The enablement requirement of 35 U.S.C. § 112, first paragraph, ensures that an application teaches how to make and use the invention as claimed without requiring undue experimentation. The inquiry may be guided by consideration of several factors enumerated in a biotechnology context in *In re Wands*.

The Applicants have amended claims 14, 16, and 17 by defining the claimed sequences with a combination of structural and/or functional characteristics taught in the specification. For example, the variants of claim 14 all possess a recited sequence relationship to SEQ ID NO: 2, namely "at least 95 percent identical to the amino acid sequence of SEQ ID NO: 2, wherein the polypeptide has human E3α ligase activity of the polypeptide set forth in SEQ ID NO: 2." The application also teaches one how to make and use such variants without undue experimentation (*see* the specification at page 27, line 29, through page 33). The application describes methods of determining identity and similarity, and teaches methods of making conservative and non-conservative amino acid modification. For example, the application explains how conservative modifications to the amino acid sequence (and the corresponding modifications to the encoding nucleotides) will produce human E3 α ubiquitin ligase polypeptides having functional and chemical characteristics similar to those of naturally occurring human E3 α ubiquitin ligase polypeptides.

The Applicants have also amended claim 16 to recite an isolated polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2 with modifications of one to 100 amino acids consisting of amino acid substitutions, amino acid insertions, amino acid deletions, C-terminal truncations, and/or N- terminal truncations up to about 100 amino acids, wherein the polypeptide has human E3 α ubiquitin ligase activity of the polypeptide set forth in SEQ ID NO: 2, thus providing structural and functional characteristics sufficient to identify members of the claimed genus. Support in the specification for variants of human E3α ubiquitin ligase polypeptide with modifications of from one to 100 amino acids is found at page 17, lines 14-32. The specification teaches that variants may be naturally occurring or artificially constructed. The specification also teaches that such variants may be prepared from the corresponding nucleic acid molecules encoding them. Likewise, support in the specification for human E3α ubiquitin ligase activity is found at page 2, line 8, through page 4, line 14, wherein the specification describes how E3α ubiquitin ligase functions in the proteosomal pathway.

Claim 17 has been amended to recite the stringent conditions necessary for hybridization and to define the type of polypeptide activity (human E3α ubiquitin ligase activity) exhibited by the claimed genus of polypeptides, thus providing structural and functional characteristics sufficient to identify members of the claimed genus. The specification teaches various stringent hybridization conditions and provides references for carrying out experiments involving hybridization (*see* page 14, line 27, through page 16, line 20).

Given the base sequence information (e.g., SEQ ID NO: 2), the specifically identified activity of the molecules (*i.e.*, human E3α ubiquitin ligase activity), and the well-known techniques for detecting such activity, the Applicants submit that one skilled in the art would be able to identify and make the claimed variants of the native human E3α ubiquitin ligase using no more than routine experimentation.

In view of the foregoing comments and the amendments to the claims, the Applicants submit that claims 14, 16-18, 40-45, 49, and 50 are fully enabled by the present specification and the rejection of the claims under 35 U.S.C. § 112, first paragraph, should be withdrawn.

C. The Rejections Under 35 U.S.C. § 112, Second Paragraph, May Properly Be Withdrawn.

Claims 14, 16-18, 40-45, 49, and 50 were rejected under 35 U.S.C § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as their invention. Specifically, the claims were rejected for assertedly: 1) not defining the metes and bounds of the clause "the mature amino acid sequence as set forth in SEQ ID NO: 2 comprising a mature amino terminus at residue 1, optionally further comprising an amino terminal methionine" in claim 14(a) because SEQ ID NO: 2 already contains a methionine at position 1 and claim 42 recites "the mature amino acid sequence as set forth in SEQ ID NO: 2;" 2) reciting "the polypeptide has an activity of the polypeptide set forth in SEQ ID NO: 2" in claims 14 and 16 without defining the activity; 3) reciting "highly stringent conditions" in claim 17 and defining these conditions by non-limiting examples rendering the metes and bounds of claim 17 unascertainable (pages 14-16 of the specification); 4) not defining the degree of complementarity in claim 17(d); 5) being redundant when reciting "the coding sequence" in claim 17(c) because SEQ ID NO: 1 comprises both coding sequence and its complement; and 6) lacking clarity in claim 44 because it is not clear as to which of the two polypeptides recited in base claim 43 is covalently modified by a water-soluble polymer, an because the term "derivative" is defined by non-limiting examples. In response, the Applicants respectfully traverse this rejection. Moreover, this rejection for indefiniteness is now moot in consideration of the amendments to the claims.

Claim 14 has been amended to delete the asserted indefinite subpart 14(a). Claims 14, 16, and 17 have been amended to recite a specific activity for the polypeptide set forth in SEQ ID NO: 2, *i.e.*, "E3α ligase activity." Claim 17 has been amended to provide specific conditions required for stringent hybridization. Claim 17 has been amended to recite that the nucleotide sequence of part (d) should be <u>fully</u> complementary to any of (a)-(c). Claim 17 has been amended to state that a nucleotide sequence of 17(c) should hybridize under highly stringent conditions to the complement of <u>the coding sequence of</u> parts (a) or (b). Last, claim 43 has been amended to recite "chemically modified derivative" and claim 44 has been amended to depend on the polypeptide derivative of claim 43. The amendments to claims 14, 16, 17, 43, and 44 have rendered moot the rejections under 35 U.S.C. § 112, second paragraph, as applied to these claims. Dependent claims incorporate the limitations of the base claims from which they

depend. Accordingly dependent claims 18, 40-42, 45, 49, and 50 have been clarified by the clarifying amendments to claims 14, 16, 17, 43, and 44.

In view of the foregoing comments and the amendments herein, the rejection of claims 14, 16-18, 40-45, 49, and 50 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

III. Conclusion

In view of the amendments and remarks provided herein, the Applicants submit that the claims are in condition for allowance and early notification thereof is respectfully requested. Should the Examiner wish to discuss any aspect of the present application, she is urged to contact the undersigned at the telephone number provided below.

Dated: May 8, 2006

Respectfully submitted,

By _____

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NCBI **Blast 2 Sequences results**

PubMed Entrez BLAST OMIM Taxonomy Structure

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.12 [Aug-07-2005]

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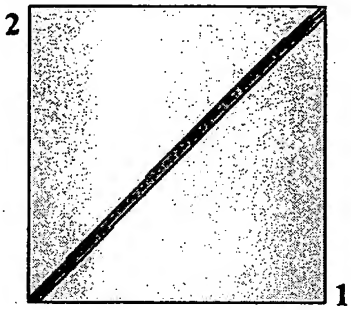

NOTE:Bitscore and expect value are calculated based on the size of the nr database.

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Gapped
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  TITLE     Direct Submission
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FIG. 2

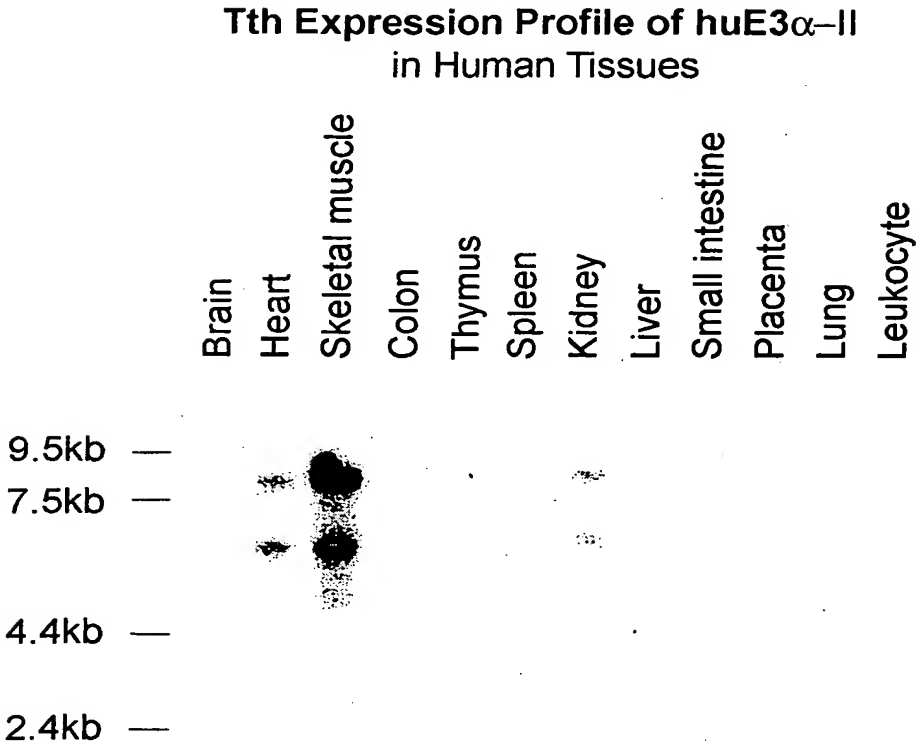

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FIG. 3

Tth Expression Profile of huE3α-I in Human Tissues

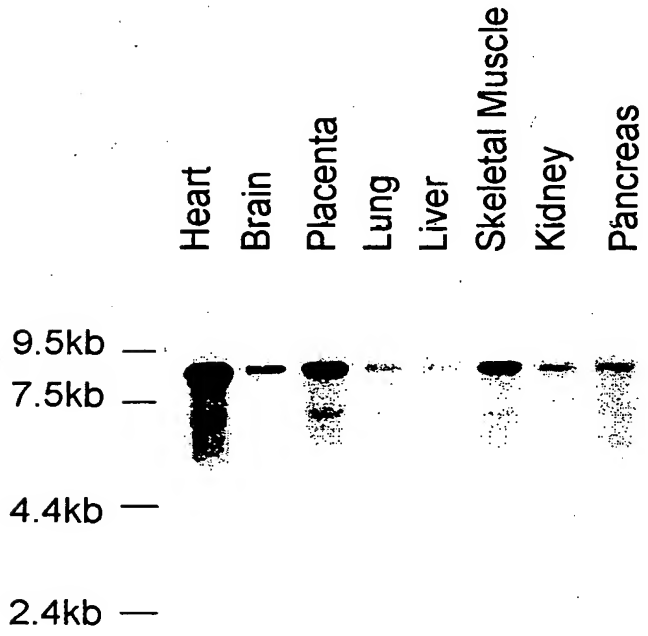


Figure 4
Ubiquitination of Endogenous Proteins

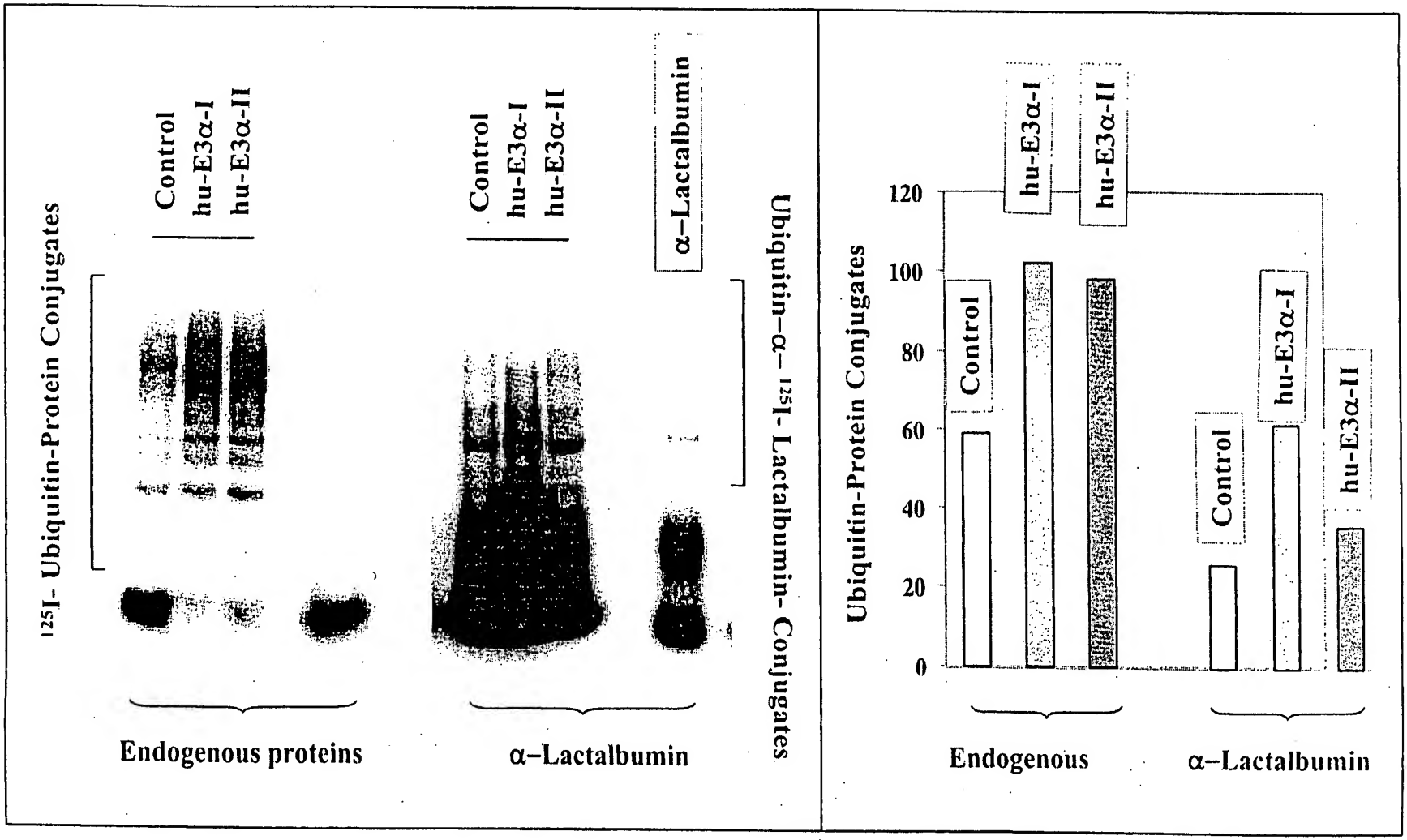
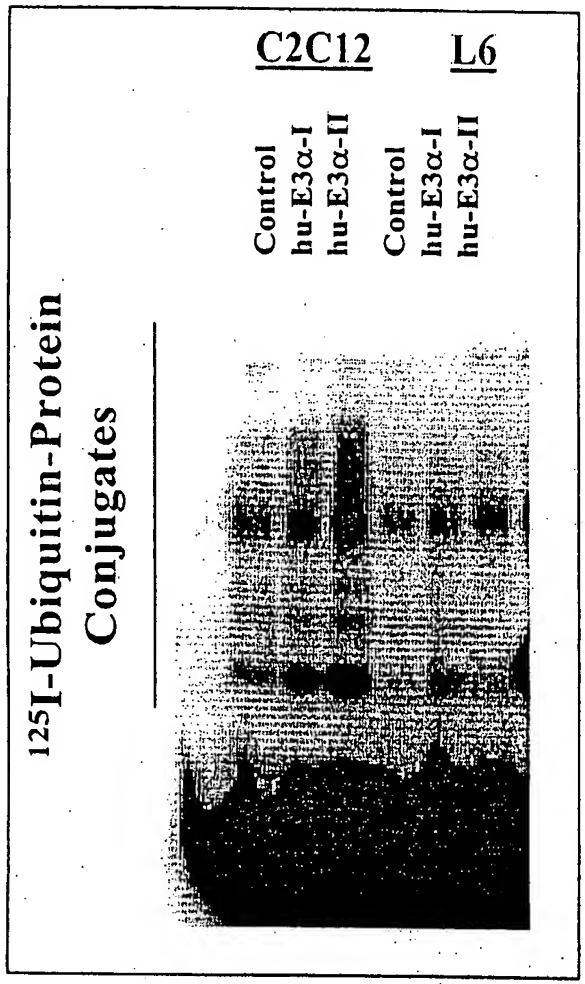


Figure 5

Transfection of Human E3a-I or E3a-II cDNA Stimulates Ubiquitin Conjugation in Cultured Muscle Cell Lines



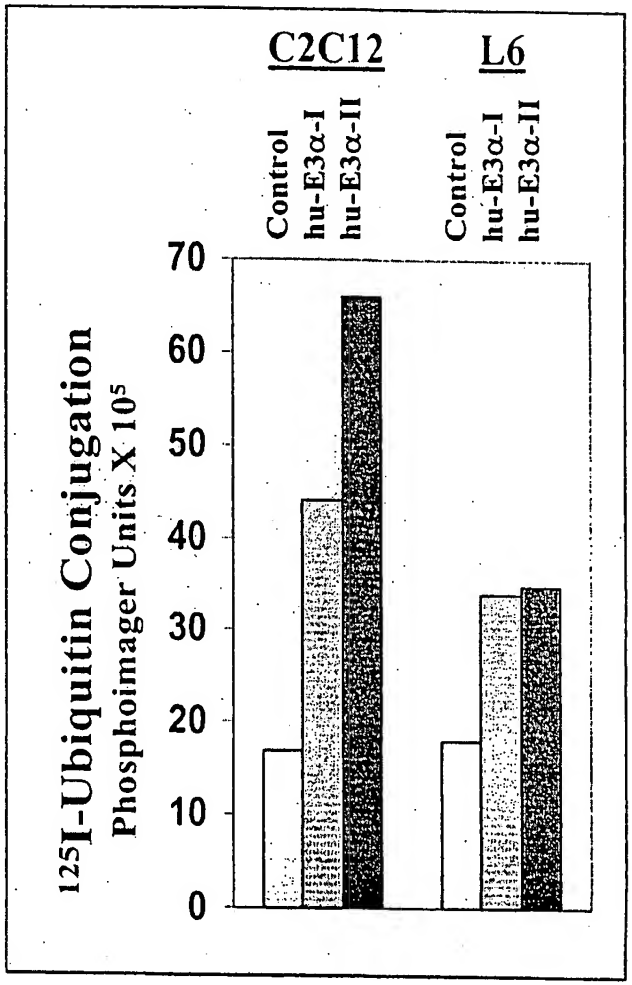


Figure 6

^{125}I-Ubiquitin Conjugation to Muscle Proteins and Its Sensitivity to E3α Inhibitor in Skeletal Muscle Extracts

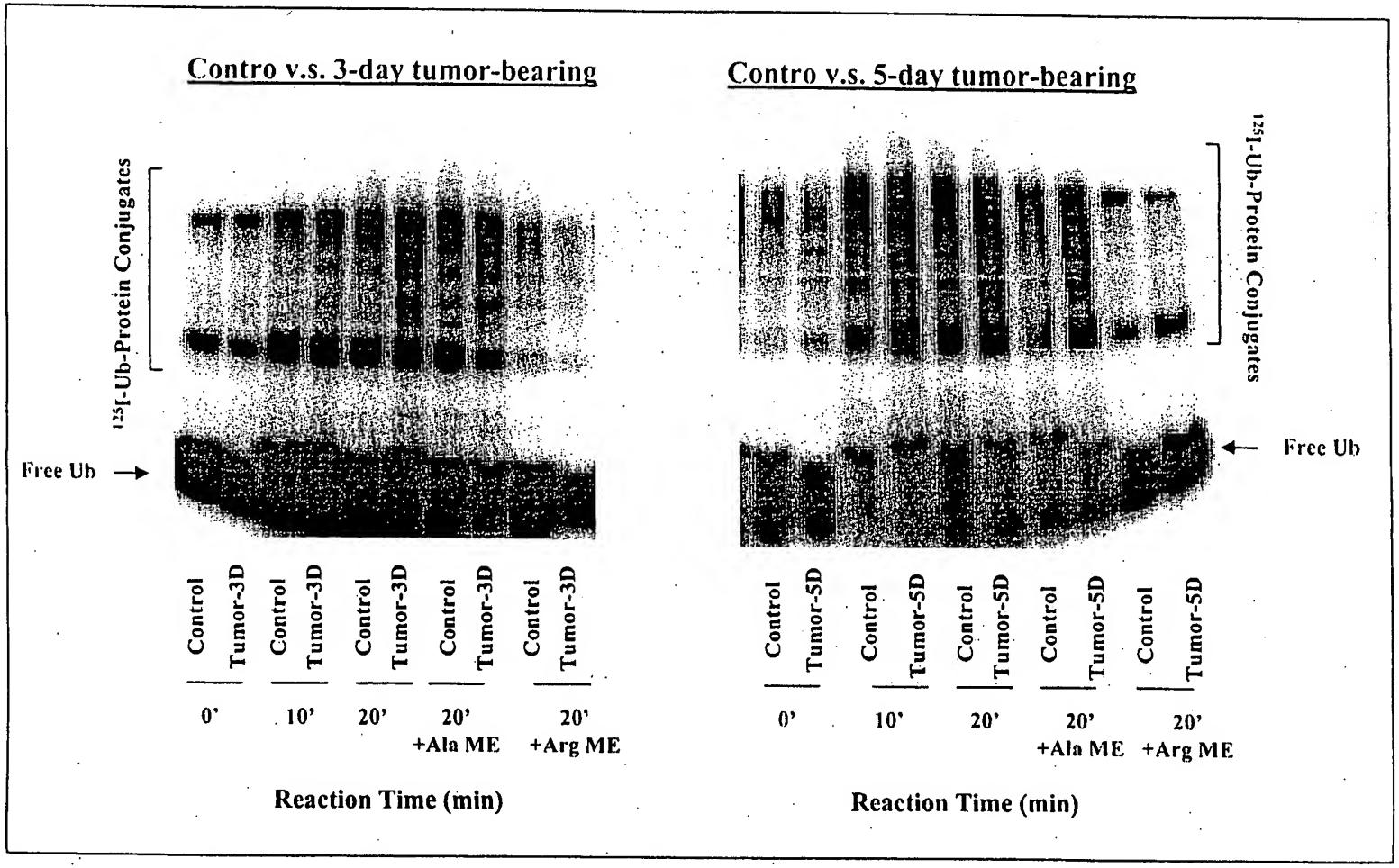


Figure 7

Rates of Ubiquitination of N-end Rule Substrate α-Lactalbumin in Skeletal Muscle Extracts

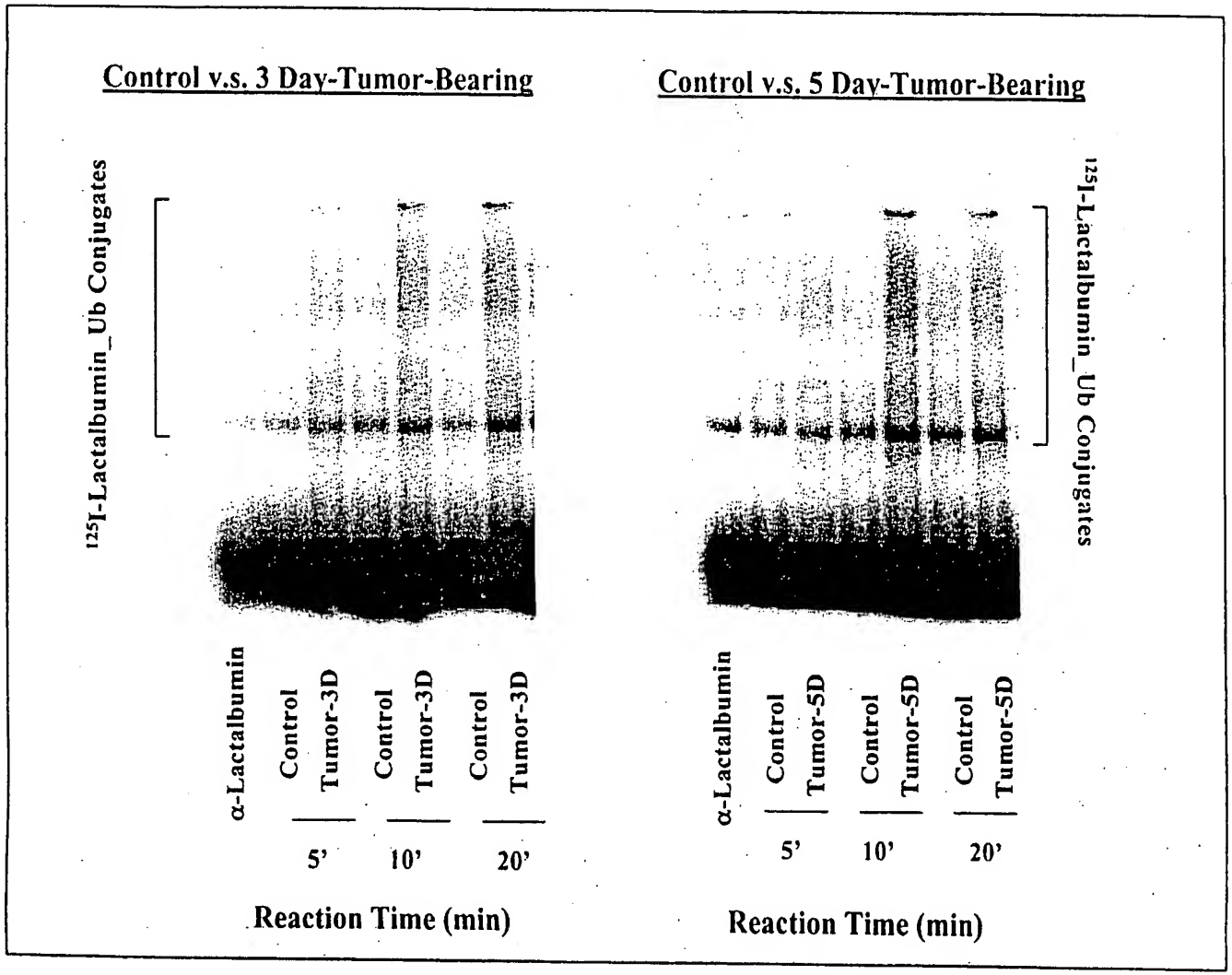


Figure 8

Northern blot analysis of E3α-I & E3α-II expression in gastrocnemius muscles in YAH-130 exprimental cachexia model

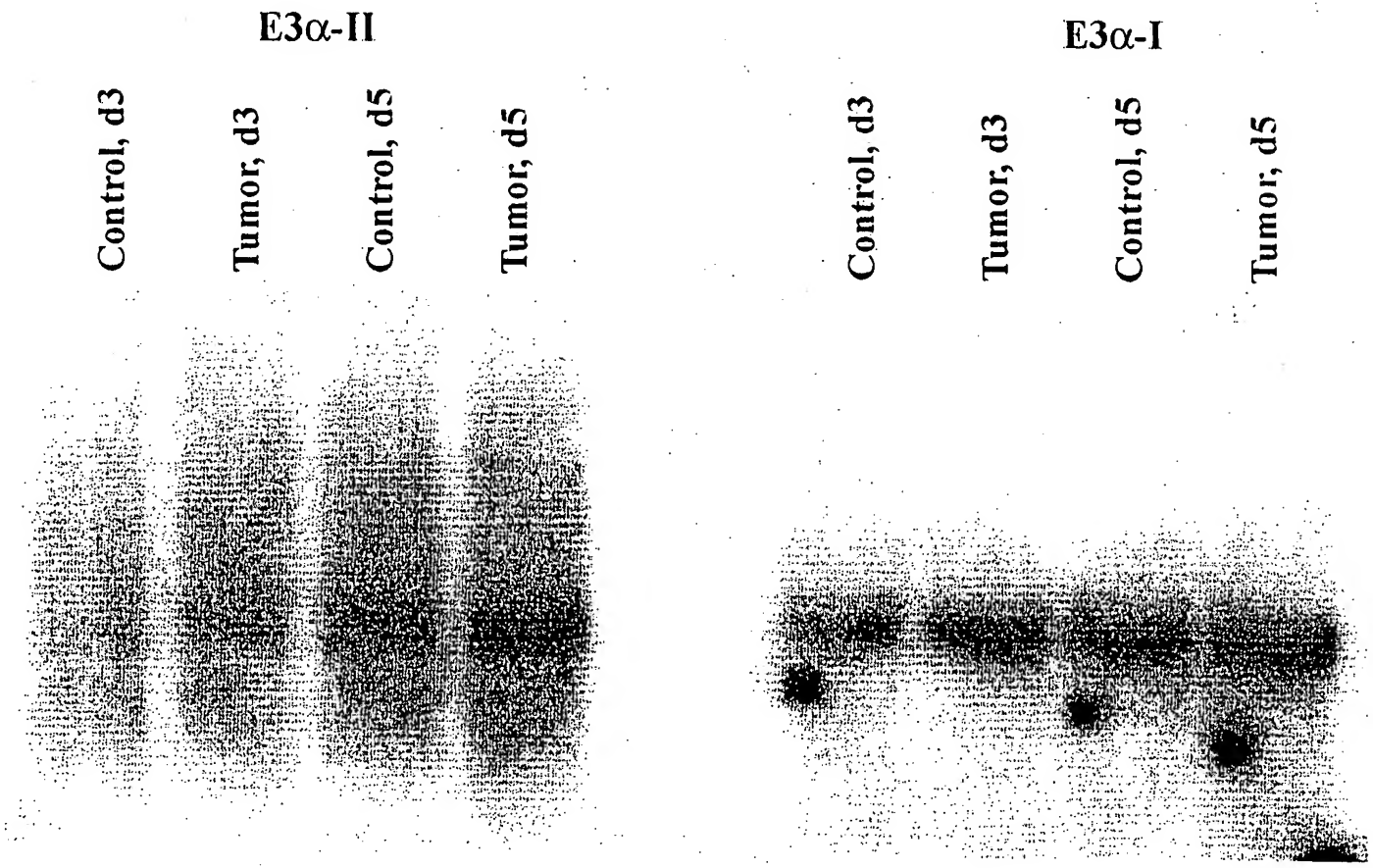


Figure 9

Northern blot analysis of E3α-I and E3α-II expression in gastrocnemius muscle and cardiac muscle in C26 experimental cachexia model

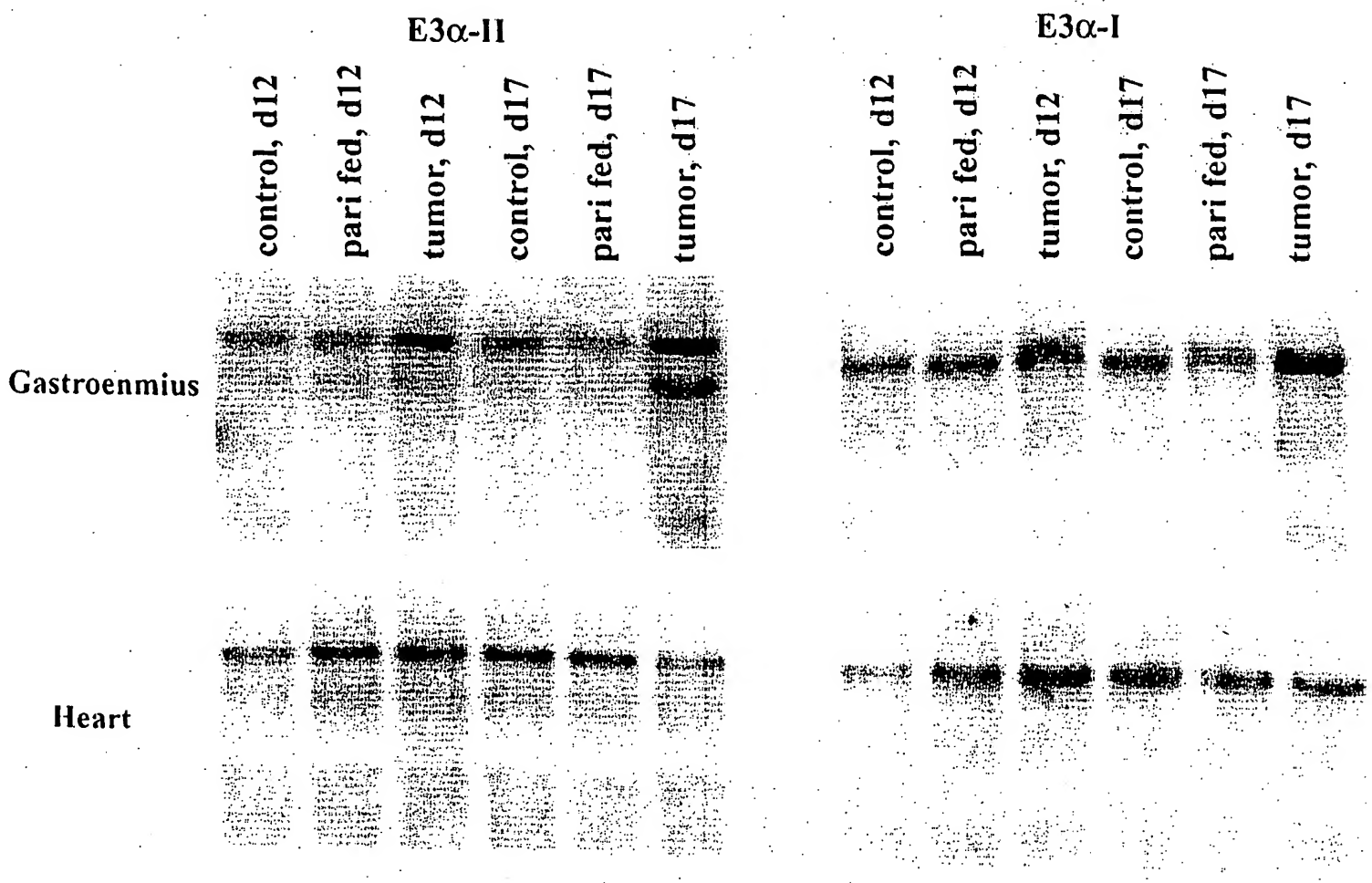


Figure 10

Proinflammatory cytokines TNF-α and IL-6 induce E3α-II Expression in C2C12 myostube culture

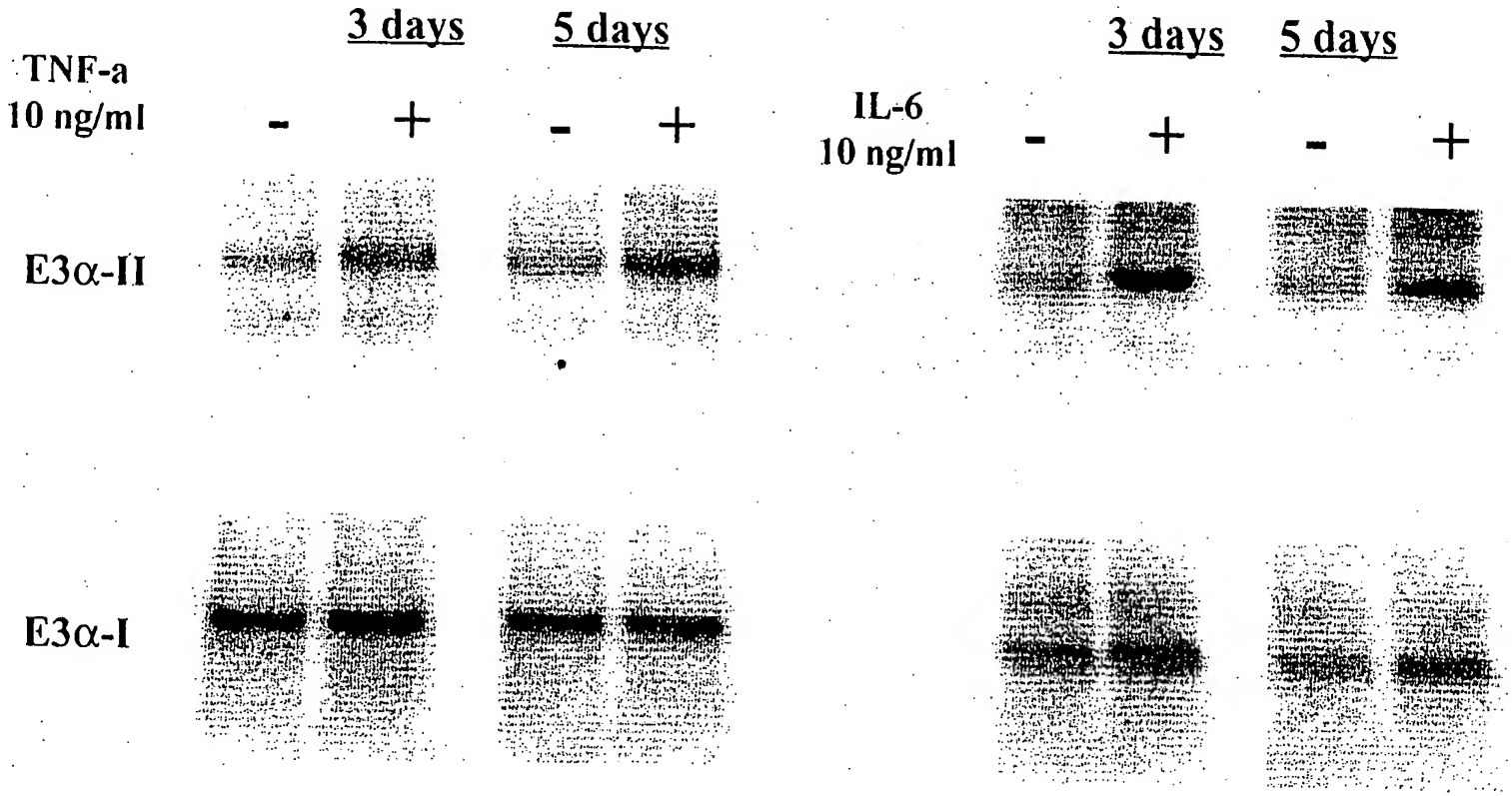


Figure 11

IL-6 Elicits Accelerated Ubiquitination in C2C12 Myotube Cultures

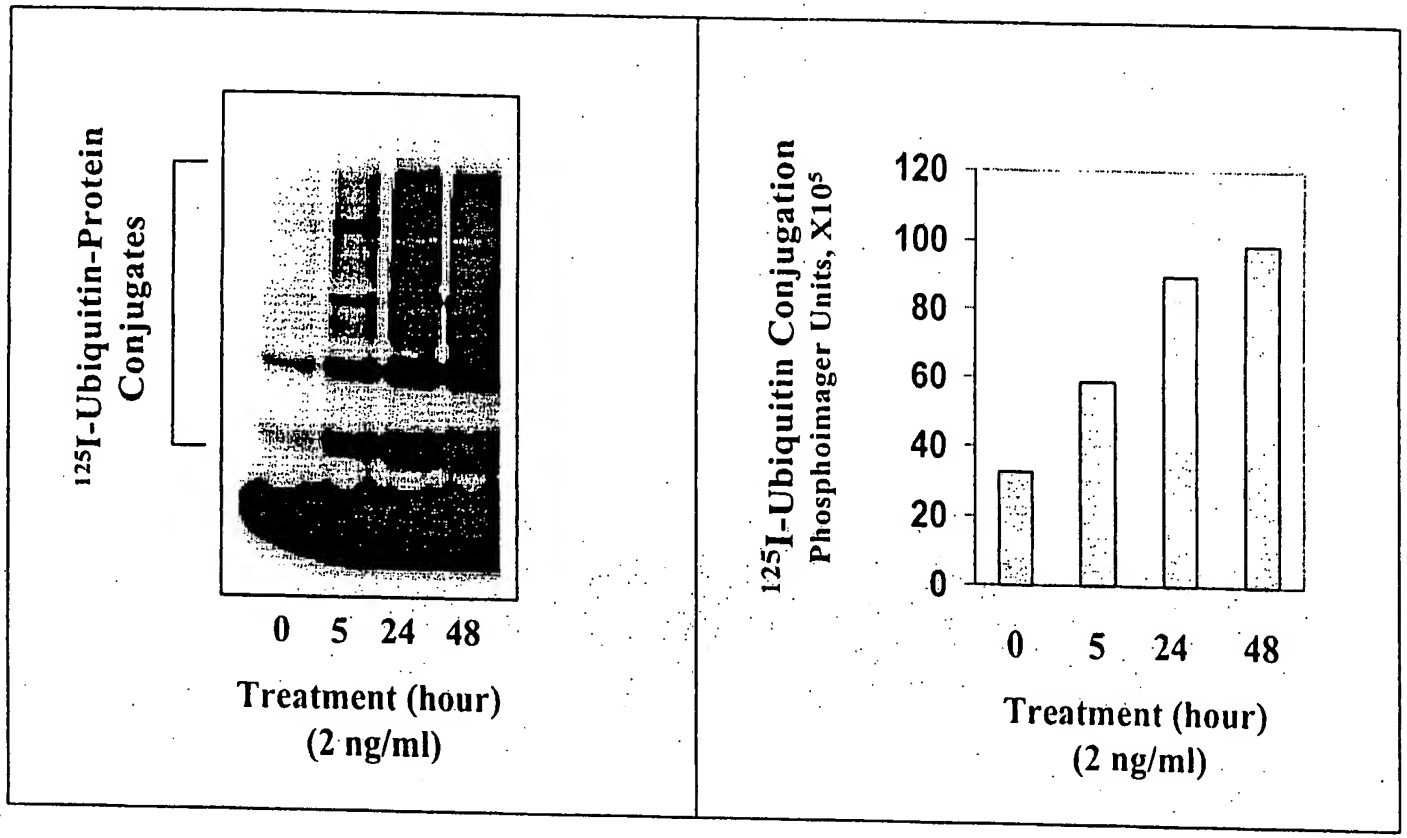
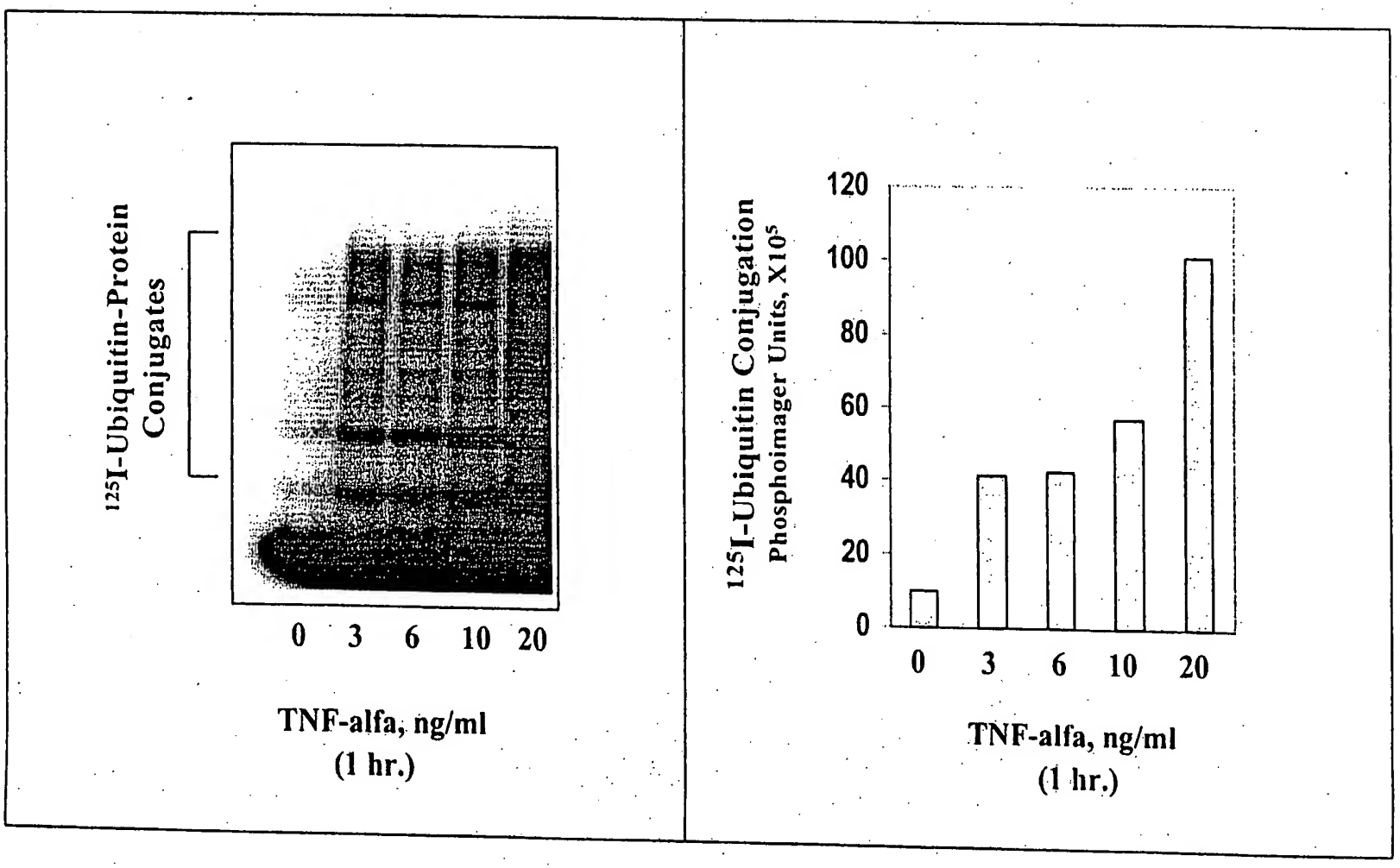


Figure 12

TNFα Elicits Accelerated Ubiquitination in C2C12 Myotube Cultures



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